Medical Policy

Subject:	Subcutaneous Hormone Replacement Implants		
Document #:	DRUG.00031	**Publish Date:**	02/28/2018
Status:	Revised	**Last Review Date:**	01/25/2018

Description/Scope

This document addresses indications for the use of subcutaneous hormone *implants* for the treatment of hormone deficit conditions. This document does not address the use of hormone implants for treatment of other indications for example contraception or treatment of cancer.

Note: This document addresses subcutaneous hormone implants only. This document does not address other formulations of testosterone, such as oral (pill and sublingual), topical (for example, gels), or injectable (intramuscular) medication products.

Please see the following documents for additional information on related topics:

- CG-DRUG-11 Infertility Drugs
- CG-DRUG-59 Testosterone Injectable
- CG-SURG-27 Sex Reassignment Surgery

Position Statement

Medically Necessary:

Symptomatic Hypogonadism (Primary or Secondary) in Adults:

I. Subcutaneous testosterone implants used for the initiation of hormone replacement therapy are considered **medically necessary** when **ALL** of the following criteria are met (A, B, C, D and E):
   A. Individual is male; **and**
   B. Individual is 18 years of age or older; **and**
   C. Prior to starting testosterone therapy, an initial and a repeat (at least 24 hours apart) morning total testosterone level is provided to confirm a low testosterone serum level indicating **one** of the following (1 or 2);
      1. Individual is 70 years of age or younger with a serum testosterone level of less than 300 ng/dL; **or**
      2. Individual is over 70 years of age with a serum testosterone level of less than 200 ng/dL; **and**
   D. Individual has documentation of **one** of the following conditions (1 or 2):
      1. Primary hypogonadism (congenital or acquired) (for example, bilateral torsion**,** cryptorchidism**,** chemotherapy**,** Klinefelter Syndrome**,** orchitis, orchiectomy, toxic damage from alcohol or heavy metals, vanishing testis syndrome, idiopathic primary hypogonadism, age-related hypogonadism [also referred to as late-onset hypogonadism]);
      or

2. Hypogonadotropic hypogonadism (also called secondary hypogonadism) (congenital or acquired) (for example, idiopathic gonadotropic or luteinizing hormone-releasing hormone [LHRH] deficiency, pituitary-hypothalamic injury); **and**

E. Individual presents with symptoms associated with hypogonadism, such as, but not limited to at least **one** of the following (1 through 9):
1. Reduced sexual desire (libido) and activity; **or**
2. Decreased spontaneous erections; **or**
3. Breast discomfort/gynecomastia; **or**
4. Loss of body (axillary and pubic) hair, reduced need for shaving; **or**
5. Very small (especially less than 5 mL) or shrinking testes; **or**
6. Inability to father children or low/zero sperm count; **or**
7. Height loss, low trauma fracture, low bone mineral density; **or**
8. Hot flushes, sweats; **or**
9. Other less specific signs and symptoms including decreased energy, depressed mood/dysthymia, irritability, sleep disturbance, poor concentration/memory, diminished physical or work performance.

II. Subcutaneous testosterone implants used for continuation of hormone replacement therapy are considered **medically necessary** when the criteria for initial therapy were met and **ALL** the following are met (A, B, and C):
A. Individual met all diagnostic criteria for initial therapy; **and**
B. Individual has had serum testosterone level measured in the previous 180 days; **and**
C. Individual has obtained clinical benefits as noted by symptom improvement.

Delayed Puberty:

III. Subcutaneous testosterone implants are considered **medically necessary** for the treatment of delayed puberty when **ALL** of the following criteria are met (A, B, and C):
A. Individual is a male 14 years of age or older; **and**
B. Individual is using hormone to stimulate puberty; **and**
C. Documentation is provided indicating few to no signs of puberty.

Gender Reassignment:

IV. Subcutaneous testosterone implants are considered **medically necessary** for transgender individuals when **ALL** of the following criteria are met (A, B and C):
A. Individual is 16 years of age or older; **and**
B. Individual has a diagnosis of gender dysphoria/incongruence or gender identity disorder; **and**
C. The goal of treatment is female-to-male gender reassignment.

Investigational and Not Medically Necessary:

Subcutaneous testosterone implants are considered **investigational and not medically necessary** for all indications not listed above.

Subcutaneous hormone implants (estrogen alone OR estrogen combined with testosterone) are considered **investigational and not medically necessary** for the treatment of hormone deficit conditions, including but not limited to:

1. Hormone replacement therapy (HRT) for female menopause;
2. Delayed puberty in females.

Rationale

Testosterone pellets:

Testosterone is an androgen hormone responsible for normal growth and development of male sex characteristics. In certain medical conditions such as hypogonadism, the endogenous level of testosterone falls below normal levels. Primary hypogonadism includes conditions such as testicular failure due to cryptorchidism, bilateral torsion, orchitis, or vanishing testis syndrome; bilateral orchidectomy; and inborn errors in the biosynthesis of testosterone. Secondary hypogonadism, also called hypogonadotropic hypogonadism includes conditions such as gonadotropin-releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury resulting from tumors, trauma, surgery, or radiation.

Testosterone hormone replacement can be delivered by mouth, intramuscular injection, topically, buccally or subcutaneously by testosterone pellets. Testosterone pellets have been approved by the U.S. Food and Drug Administration for the treatment of congenital or acquired androgen deficiency as a result of primary or secondary hypogonadism, or delayed puberty (Product information label, 2016).

According to the American Association of Clinical Endocrinologists (AACE) medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult males (2002 update):

> Hypogonadism may manifest with testosterone deficiency, infertility, or both conditions. Symptoms of hypogonadism depend primarily on the age of the male patient at the time of development of the condition. Hypogonadism is often unrecognized before the age of puberty unless it is associated with growth retardation or other anatomic or endocrine abnormalities.
>
> When hypogonadism develops before the age of puberty, the manifestations are those of impaired puberty (for example, gynecomastia; small testes, phallus and prostate; scant pubic and axillary hair; reduced male musculature; persistent high-pitched voice)… Post-pubertal loss of testicular function results in slowly evolving subtle clinical symptoms and signs… Adult males with hypogonadism may exhibit progressive loss of muscle mass; loss of libido; impotence; and oligospermia or azoospermia… In aging men, these symptoms and signs may be difficult to appreciate because they are often attributed to getting older… Hormonal and ancillary testing should be performed to allow pertinent treatment considerations. Testosterone replacement therapy can often enable the patient to function in a more normal manner and decrease the risk of future problems with fertility, mood disturbances, fatigue, impaired virilization, and osteoporosis.
>
> Further studies are needed to determine the influence of testosterone replacement therapy on cardiovascular risk… The ultimate goals are to improve not only the duration but also the quality of life and to allow people to reach their full potential regardless of age.

The Endocrine Society published clinical practice guidelines on Testosterone Therapy in Men with Androgen Deficiency in 2006, with an update published in 2010 (Bhasin). The 2010 guidelines included the following statements for the diagnosis of androgen deficiency and therapy with testosterone replacement:

- We recommend making the diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels. (Strong recommendation; very low quality of evidence);
- We recommend testosterone therapy for symptomatic men with classical androgen deficiency syndromes aimed at inducing and maintaining secondary sex characteristics and at improving their sexual function, sense of well-being, and bone mineral density (Strong recommendation; low quality of evidence);
- We recommend against testosterone therapy in patients with breast or prostate cancer. (Strong recommendation; quality of evidence very low for breast cancer, low for prostate cancer);
- We recommend that clinicians assess prostate cancer risk in men being considered for testosterone therapy. (Strong recommendation; very low quality of evidence);
- We suggest initiating testosterone therapy with any of the following regimens (75 to 100 mg of testosterone enanthate or cypionate administered IM weekly, or 150 to 200 mg administered every 2 weeks, injectable testosterone undecanoate; also patches, gel, buccal tablets, implanted pellets) chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost. (Weak recommendation; strength of evidence low).

In 2015, the Endocrine Society added the following amended recommendations:

- Men with metabolic syndrome, who were previously unexamined by the 2010 Endocrine Society Clinical Practice Guidelines, may benefit from testosterone replacement therapy (TRT) based on improvements in biometrics and insulin sensitivity. Effects of TRT on similar endpoints in men with type 2 diabetes mellitus remain unclear;
- Effects of TRT on erectile function, even in men refractory to phosphodiesterase type 5 inhibitors, and on quality of life in men with erectile dysfunction remain inconclusive (Seftel, 2015).

An established diagnosis of hypogonadism with androgen deficiency includes appropriate evaluation and diagnostic workup of a man who presents with symptoms of hypogonadism. Clinical Practice Guidelines recommend measuring serum testosterone only in men with consistent clinical manifestations of hypogonadism. Screening in asymptomatic populations is not recommended. Measurement of serum total testosterone is initially used; serum-free testosterone levels can be measured when total testosterone is in the low normal range and alterations of serum hormone-binding globulin are suspected. Once a persistently low testosterone level has been established, diagnostic testing of the hypothalamic-pituitary axis should be performed to distinguish primary hypogonadism from secondary hypogonadism. When secondary hypogonadism is identified, the underlying etiology should be identified, and any reversible causes treated appropriately prior to consideration of testosterone replacement.

Persistently low testosterone levels refers to serum levels that are below the lower limit of normal on at least two occasions when measured in the early morning. The threshold lower limit for serum testosterone levels is not standardized. The Endocrine Society recommends that a lower limit for normal levels is 300 ng/dL for total testosterone and 9.0 ng/dL for free testosterone… We suggest monitoring testosterone levels 3 to 6 months after initiation of testosterone therapy

> and then annually to assess whether symptoms have responded to treatment and whether the individual is suffering from any adverse effects. Therapy should aim to raise the serum testosterone level into the mid-normal range. For injectable testosterone enanthate or cypionate: measure serum testosterone level midway between injections. If testosterone is > 700 ng/dl (24.5 nmol/liter) or < 400 ng/dl (14.1 nmol/liter), adjust dose or frequency. Testosterone pellets, measure testosterone levels at the end of dosing intervals. Adjust the number of pellets and/or the dosing interval to achieve serum testosterone levels in the normal range. (Bhasin, 2010)

The Endocrine Society also provided the following list of specific symptoms of hypogonadism:

- Incomplete or delayed sexual development;
- Decreased libido;
- Decreased spontaneous erections;
- Breast discomfort, gynecomastia;
- Loss of axillar and/or pubic body hair;
- Very small (<5 mL) or shrinking testes;
- Infertility due to low sperm count;
- Height loss due to vertebral fractures, low trauma fractures, low bone density;
- Hot flushes, sweats (Bhasin, 2010).

Regarding hypogonadism associated with male aging, in 2009 the International Society for the Study of Aging Male, the International Society of Andrology, the European Association of Urology, the European Academy of Andrology, and the American Society of Andrology issued joint guidelines on the treatment and monitoring of late-onset hypogonadism which provided the following:

> The diagnosis of treatable hypogonadism requires the presence of symptoms and signs suggestive of testosterone deficiency (Grade A recommendation; level of evidence 3). The symptom most associated with hypogonadism is low libido (Grade A recommendation; level of evidence 3). Other manifestations of hypogonadism include erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality, and depressed mood. None of these symptoms are specific to the low androgen state but may raise suspicion of testosterone deficiency. One or more of these symptoms must be corroborated with a low serum testosterone level (Grade A recommendation; level of evidence 3).
>
> Presentations of natural testosterone should be used for substitution therapy. Currently available intramuscular, subdermal, transdermal, oral, and buccal preparations of testosterone are safe and effective (Grade A recommendations; level of evidence 1b). The selection of the preparation should be a joint decision of an informed patient and physician (Wang, 2009).

The FDA issued the following safety announcement that included the following information related to testosterone treatment for low testosterone associated with aging:

> The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man's symptoms seem related to low testosterone. We are requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications. Testosterone is FDA-approved as replacement therapy only for men

> who have low testosterone levels due to disorders of the testicles, pituitary gland, or brain that cause a condition called hypogonadism. Examples of these disorders include failure of the testicles to produce testosterone because of genetic problems, or damage from chemotherapy or infection. However, FDA has become aware that testosterone is being used extensively in attempts to relieve symptoms in men who have low testosterone for no apparent reason other than aging. The benefits and safety of this use have not been established (FDA, 2016).

The FDA announcement was criticized in an American Association of Clinical Endocrinologists and American College of Endocrinology 2015 Position Statement (ref: https://www.aace.com/files/position-statements/ep14434ps.pdf) as being "too vague to be clinically meaningful". The AACE/ACE recommends that "the decision to replace testosterone therapy should be guided by the signs/symptoms and testosterone concentrations rather than the underlying cause", advising practicing clinicians to "be extra cautious in the symptomatic elderly with demonstrably low testosterone levels prior to embarking on replacement therapy and to avoid treatment of the frail elderly altogether."

The Endocrine Society Clinical Practice Guideline for Endocrine Treatment of Transsexual Persons recommends that adolescents who fulfill eligibility and readiness criteria for gender reassignment initially undergo treatment to suppress pubertal development which should be initiated at about the age of 16 years, using a gradually increasing dose schedule of cross-sex steroids (Hembree, 2009).

According to Newfield and colleagues (2006):

> Masculinizing hormone therapy (the administration of exogenous endocrine agents to induce masculinizing changes) is a medically necessary intervention for many transsexual, transgender, and gender nonconforming individuals with gender dysphoria… In FTM patients, the following physical changes are expected to occur: deepened voice, clitoral enlargement (variable), growth in facial and body hair, cessation of menses, atrophy of breast tissue, and decreased percentage of body fat compared to muscle mass.

Although secondary or tertiary hormonal treatments with androgens are indicated for palliation therapy in post-menopausal women with metastatic breast cancer, subcutaneous testosterone implants are not indicated for these uses and should not be used by females.

In 2017, the Endocrine Society updated its guideline for Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons (Hembree, 2017), in which the terminology was updated to "Gender Dysphoria/Gender Incongruence (GD/gender incongruence)." The following recommendations were made to amend the earlier recommendations:

- GD/gender-incongruent persons seek and/or are referred to endocrinologists to develop the physical characteristics of the affirmed gender. They require a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender.
- Hormone treatment is not recommended for prepubertal GD/gender-incongruent persons.
- Those clinicians who recommend gender-affirming endocrine treatments should be appropriately trained diagnosing clinicians (required), a mental health provider for adolescents (required) and a mental health

professional for adults (recommended), and should be knowledgeable about the diagnostic criteria and criteria for gender-affirming treatment, have sufficient training and experience in assessing psychopathology, and be willing to participate in the ongoing care throughout the endocrine transition.

- We recommend treating GD/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with GnRH agonists.
- Clinicians may add gender-affirming hormones after a multidisciplinary team has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment.
- Most adolescents have this capacity by age 16 years old. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age.
- For the care of peripubertal youths and older adolescents, we recommend that an expert multidisciplinary team comprised of medical professionals and mental health professionals manage this treatment.
- We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment.
- For adult GD/gender-incongruent persons, the treating clinicians (collectively) should have expertise in transgender-specific diagnostic criteria, mental health, primary care, hormone treatment, and surgery, as needed by the patient. We suggest maintaining physiologic levels of gender-appropriate hormones and monitoring for known risks and complications.
- When high doses of sex steroids are required to suppress endogenous sex steroids and/or in advanced age, clinicians may consider surgically removing natal gonads along with reducing sex steroid treatment.
- Clinicians should monitor both transgender males (female to male) and transgender females (male to female) for reproductive organ cancer risk when surgical removal is incomplete.
- Clinicians should persistently monitor adverse effects of sex steroids.
- Physicians should educate transgender persons regarding the time course of steroid-induced physical changes.
- Clinicians should avoid harming individuals (via hormone treatment) who have conditions other than GD/gender incongruence and who may not benefit from the physical changes associated with this treatment.

The updated Endocrine Society guidelines document contains additional information about long-term care and monitoring for adverse outcomes prevention and about surgical options when being considered:

> We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country (Hembree, 2017).

In May 2013, the American Psychiatric Association published an update to their Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5). This update included a significant change to the nomenclature of conditions related to gender psychology. Specifically, the term "Gender Identity Disorder (GID)" was replaced with "Gender Dysphoria." Additionally, the DSM-5 provided updated diagnostic criteria for gender dysphoria for both children and adults. The new criteria are as follows:

Gender dysphoria in Children*

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months duration, as manifested by at least six of the following (one of which must be Criterion A1):
   1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender, different from one's assigned gender).
   2. In boys (assigned gender), a strong preference for cross dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to wearing of typical feminine clothing.
   3. A strong preference for cross-gender roles in make-believe play of fantasy play.
   4. A strong preference for toys, games, or activities stereotypically used or engaged in by the other gender.
   5. A strong preference for playmates of the other gender.
   6. In boys (assigned gender), a strong rejection of typically masculine toys, games and activities and a strong avoidance of rough and tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games and activities.
   7. A strong dislike of one's sexual anatomy.
   8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.0 [E34.50] androgen insensitivity syndrome).
Coding note: Code the disorder of sex development as well as gender dysphoria.

Gender dysphoria in Adolescents and Adults*

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months duration, as manifested by at least two of the following:
   1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
   2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
   3. A strong desire for the primary and /or secondary sex characteristics of the other gender.
   4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
   5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
   6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.0 [E34.50] androgen insensitivity syndrome).
Coding note: Code the disorder of sex development as well as gender dysphoria.

Specify if:

Post transition: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen- namely regular cross-sex treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in the natal female).

*From: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. DSM-5. American Psychiatric Association. Washington, DC. May 2013. Page 451-459.

Estrogen:

Estrogen is a hormone that occurs naturally, or is manufactured as a synthetic steroidal or nonsteroidal compound with estrogenic activity. Estrogen is used to treat moderate to severe symptoms of female menopause. Estrogen replacement therapy (ERT) indicates the use of estrogen hormone as a single agent. Estrogen in combination with progestin is called hormone replacement therapy (HRT).

Several studies (Holland, 1995; Studd, 1994; Wahab, 1997) measured estrogen implant effect on bone density, which provided objective measurement. There have been relatively few studies in which delivery of estrogen replacement therapy using implants was directly compared with other methods of estrogen administration. However, there are no estrogen formulations for subcutaneous ERT approved by the U.S. Food and Drug Administration (FDA) at this time.

There are several randomized controlled studies and uncontrolled prospective clinical trials evaluating subcutaneous HRT. Subcutaneous HRT was compared with placebo and with oral and transdermal therapy. The studies had relatively few subjects considering the large number of women candidates for HRT. None of the studies was completely blinded. Symptom relief was largely based on subjective and participant reported results. These studies could be subject to bias based on placebo effect. Reported problems with subcutaneous HRT therapy include:

- problems with pellet removal if the therapy has to be discontinued;
- infection, extrusion and/or discomfort at the insertion site;
- fluctuating blood levels of estrogen;
- dosing is not easily adjusted;
- compliance with cyclical progesterone therapy in hysterectomized women; and

- the cumulative effect of 2-3 times higher estrogen blood levels over several years not seen with the oral route.

HRT for menopause has been the subject of debate. Additional research is needed to determine the optimal dosage, treatment interval and benefit to risk ratio of hormone replacement therapy as a treatment for menopause. Estrogen compounded with testosterone for subcutaneous HRT is not FDA approved. The published literature does not demonstrate safety and utility in short- or long-term therapy.

Background/Overview

Hormone therapy can be delivered subcutaneously by implantation of the drug in pellet form in the lower abdomen or buttocks. The procedure is done in a physician's office with the use of a local anesthetic and a small incision for insertion. The release of the drug continues over a 3-6 month period, eliminating individual compliance with dosing schedules. Since the drug bypasses the gastrointestinal system and most liver metabolism, bioavailability can be increased. Sustained release can mimic endogenous production achieving therapeutic blood levels.

According to the American Association of Clinical Endocrinologists (AACE, 2002), men with decreased testosterone levels may experience a higher incidence of osteoporosis, sexual dysfunction, fatigue, cardiovascular disease and disturbances in mood.

Testosterone (Testopel®):

The following are contraindications and warnings from the Product Information Label (2016):

Contraindications

Androgens are contraindicated in men with carcinomas of the breast or with known or suspected carcinomas of the prostate. If administered to pregnant women, androgens cause virilization of the external genitalia of the female fetus. The virilization includes clitoromegaly, abnormal vaginal development, and fusion of genital folds to form a scrotal-like structure. The degree of masculinization is related to the amount of drug given and the age of the fetus, and is most likely to occur in the female fetus when the drugs are given in the first trimester. If the patient becomes pregnant while taking these drugs she should be apprised of the potential hazard to the fetus.

Warnings:

- In patients with breast cancer, androgen therapy may cause hypercalcemia by stimulating osteolysis. In this case, the drug should be discontinued.
- Prolonged use of high doses of androgens has been associated with the development of peliosis hepatitis and hepatic neoplasms including hepatocellular carcinoma. Peliosis hepatitis can be a life-threatening or fatal complication.
- Men treated with androgens may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.
- Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

- Gynecomastia frequently develops in patients and occasionally persists in patients being treated for hypogonadism.
- Androgen therapy should be used cautiously in healthy males with delayed puberty. The effect on bone maturation should be monitored by assessing bone age of the wrist and hand every 6 months. In children, androgen treatment may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect may result in compromised adult stature. The younger the child the greater the risk of compromising final mature height.
- The drug has not been shown to be safe and effective for the enhancement of athletic performance. Because of the potential risk for serious adverse health effects, this drug should not be used for such purpose.

Menopause occurs when the ovaries no longer produce estrogen, causing the reproductive system to shut down and female is free of menses for 1 year. The normal aging process is the usual reason for menopause. However, the loss of estrogen production may also be due to the surgical removal of the ovaries or as a result of treatment with chemotherapy.

According to the AACE (2011), although many women are asymptomatic in menopause, other women in the hypoestrogenic state may experience symptoms that may be severe and have a negative impact on quality of life. Symptoms of estrogen deficiency include hot flashes, sweating, insomnia, and vaginal dryness and discomfort. Hormone replacement therapy goals are to alleviate menopause symptoms, and include estrogen alone or estrogen in combination with testosterone. However, there are currently no implantable hormone pellets approved by the FDA for treatment of symptoms of menopause.

Definitions

Androgen: A general term for any male sex hormone.

Delayed Puberty: The absence or incomplete development of secondary sexual characteristics bounded by an age at which 95% of children of that sex and culture have initiated sexual maturation. In the United States, the upper 95th percentile for boys to initiate puberty is age 14 (an increase in testicular size being the first sign) and for girls is age 12.

Endogenous: Developing or originating within the body.

Gender Dysphoria/Incongruence (formerly Gender Identity Disorder): Discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics).

Hypogonadism: decreased functional activity of the gonads resulting clinically low testosterone levels.

Hypogonadotropic hypogonadism (congenital or acquired): Idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation.

Menopause: Cessation of menstruation in the human female.

Primary hypogonadism (congenital or acquired): also known as primary testicular failure. Common causes of primary hypogonadism include: bilateral torsion, cryptorchidism, chemotherapy, Klinefelter Syndrome, orchitis, orchiectomy, toxic damage from alcohol or heavy metals, Vanishing Testis Syndrome, idiopathic primary hypogonadism, and age-related hypogonadism (also referred to as late-onset hypogonadism).

Subcutaneous: Under the skin.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met for testosterone implants:

CPT

11980	Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin) [when specified as implantation of testosterone pellets]

HCPCS

S0189	Testosterone pellet; 75mg

ICD-10 Diagnosis

E23.0	Hypopituitarism (hypogonadotropic hypogonadism)
E29.1	Testicular hypofunction
E29.8	Other testicular dysfunction
E29.9	Testicular dysfunction, unspecified
E30.0	Delayed puberty
E89.5	Postprocedural testicular hypofunction
F64.0-F64.9	Gender identity disorders
N44.00-N44.04	Torsion of testis
N45.2	Orchitis
N46.11-N46.129	Oligospermia
N52.01-N52.9	Male erectile dysfunction
Q53.00-Q53.9	Undescended and ectopic testicle
Q55.22	Retractile testis
Q98.0-Q98.1	Klinefelter syndrome (karyotype 47 XXY/male with more than two X chromosomes
Q98.4	Klinefelter syndrome, unspecified
R68.82	Decreased libido
T88.7XXA-T88.7XXS	Unspecified adverse effect of drug or medicament

When services are Investigational and Not Medically Necessary:
For the codes listed above when criteria are not met or for the following diagnoses, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

ICD-10 Diagnosis

E28.310-E28.39	Primary ovarian failure
E28.8	Other ovarian dysfunction
E28.9	Ovarian dysfunction, unspecified
E89.40-E89.41	Postprocedural ovarian failure
N95.0-N95.9	Menopausal and other perimenopausal disorders
R53.81-R53.83	Other malaise and fatigue

When services are Investigational and Not Medically Necessary for estradiol or estradiol/testosterone implants:
When the code(s) describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

11980	Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin) [when specified as implantation of estradiol or combined estradiol/testosterone pellets]

HCPCS

J3490	Unclassified drugs [when specified as estrogen or estrogen/testosterone pellets]

ICD-10 Diagnosis

E28.310-E28.39	Primary ovarian failure
E28.8	Other ovarian dysfunction
E28.9	Ovarian dysfunction, unspecified
E30.0	Delayed puberty
E89.40-E89.41	Postprocedural ovarian failure
F64.0-F64.9	Gender identity disorders
N95.0-N95.9	Menopausal and other perimenopausal disorders
R53.81-R53.83	Other malaise and fatigue
R68.82	Decreased libido

References

Peer Reviewed Publications:
1. Anderson RA, Wallace AM, Sattar N, et al. Evidence for tissue selectivity of the synthetic androgen 7 alpha-methyl-19-nortestosterone in hypogonadal men. J Clin Endocrinol Metab. 2003; 88(6):2784-2793.
2. Buckler HM, Robertson WR, Wu FC. Which androgen replacement therapy for women? J Clin Endocrinol Metab. 1998; 83(11): 3920-3924.
3. del Carmen Cravioto M, Larrea F, Delgado NE, et al. Pharmacokinetics and pharmacodynamics of 25-mg estradiol implants in postmenopausal Mexican women. Menopause. 2001; 8(5):353-360.
4. File SE, Heard JE, Rymer J. Trough oestradiol levels associated with cognitive impairment in post-menopausal women after 10 years of oestradiol implants. Psychopharmacology (Berl). 2002; 161(1):107-112.
5. Holland EF, Leather AT, Studd JW. Increase in bone mass of older postmenopausal women with low mineral bone density after one year of percutaneous oestradiol implants. Br J Obstet Gynaecol. 1995; 102(3):238-242.

6. Howell S, Shalet S. Testosterone deficiency and replacement. Horm Res. 2001; 56 Suppl 1:86-92.
7. Kelleher S, Conway AJ, Handelsman DJ. Influence of implantation site and track geometry on the extrusion rate and pharmacology of testosterone implants. Clin Endocrinol. 2001; 55(4):531-536.
8. Kenemans P, van Unnik GA, Mijatovic V, van der Mooren MJ. Perspectives in hormone replacement therapy. Maturitas. 2001 15; 38 Suppl 1:S41-S48.
9. Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. Qual Life Res. 2006; 15(9):1447-1457.
10. Studd JWW, Holland EFN, Leather AT, Smith RNJ. The dose-response of percutaneous oestradiol implants on the skeletons of postmenopausal women. Br J Obstet Gynaecol. 1994; 101(9):787-791.
11. Suhonen SP, Allonen HO, Lähteenmäki P. Sustained-release estradiol implants and a levonorgestrel-releasing intrauterine device in hormone replacement therapy. Am J Obstet Gynecol. 1995; 172(2 Pt 1):562-567.
12. Templeman C, Quinn D, Hansen R, et al. An audit of oestrogen implant hormone replacement therapy. Aust NZ J Obstet Gynaecol. 1998; 38(4):455-460.
13. Vogelvang TE, Mijatovic V, Kamp O, et al. Neither long-term treatment with raloxifene nor hormone replacement therapy modulate cardiac function in healthy postmenopausal women: two randomized, placebo-controlled, 2-year studies. Am J Obstet Gynecol. 2002; 186(4):729-736.
14. Wahab M, Ballard P, Purdie DW, et al. The effect of long-term oestradiol implantation on bone mineral density in postmenopausal women who have undergone hysterectomy and bilateral oophorectomy. Br J Obstet Gynaecol. 1997; 104(6):728-731.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Association of Clinical Endocrinologists (AACE). AACE medical guidelines for clinical practice for the diagnosis and treatment of menopause. Endocrine Practice. 2011; 1(6):11-25.
2. American Association of Clinical Endocrinologists. AACE Medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients, 2002 update. Endocr Pract. 2002; 8(6):439-456.
3. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015; 63(11):2227-2246.
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 2013. Washington, DC. Pages 451-459.
5. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010; 95(6):2536-1559. Available at: http://press.endocrine.org/doi/full/10.1210/jc.2009-2354. Accessed on December 7, 2017.
6. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2006; 91(6):1995-2010.
7. Coleman E, Bockting W, Botzer M, et al. World Professional for Transgender Health (WPATH). Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7. Int J Transgen. 2011; 13:165-232.
8. Goodman N, Guay A, Dandona P, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on association of testosterone and cardiovascular risk. Endocr Pract. 2015; 21(9):1067-1073. Available at: https://www.aace.com/files/position-statements/ep14434ps.pdf. Accessed on December 18, 2017.
9. Hembree WC. Guidelines for pubertal suspension and gender reassignment for transgender adolescents. Child Adolesc Psychiatr Clin N Am. 2011; 20(4):725-732.

10. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine treatment of transsexual persons: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009; 94(9):3132-3154.
11. Hembree WC, Cohen-Kettenis P, Gooren L, et al.; Endocrine Society. Endocrine Treatment of Gender Dysphoric/Gender Incongruent Persons. An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2017; 102(11):1-35.
12. Seftel AD, Kathrins M, Niederberger C. Critical update of the 2010 Endocrine Society clinical practice guidelines for male hypogonadism: a systematic analysis. Mayo Clin Proc. 2015; 90(8):1104-1115.
13. Testopel. [Product Information]. Malvern, PA, Endo Pharmaceuticals Inc. October 2016. Available at: http://www.endo.com/File%20Library/Products/Prescribing%20Information/Testopel_prescribing_information.pdf. Accessed on December 7, 2017.
14. Testosterone. DrugPoints® System (electronic version). Truven Health Analytics, Greenwood Village, CO. Updated June 9, 2016. Available at: http://www.micromedexsolutions.com. Accessed on December 7, 2017.
15. Testosterone Monograph. Lexicomp® Online, American Hospital Formulary Service® (AHFS®) Online, Hudson, Ohio, Lexi-Comp., Inc. Last revised October 25, 2016. Accessed on June 25, 2017.
16. U.S. Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging. 2015. Available at: https://www.fda.gov/downloads/Drugs/DrugSafety/UCM436270.pdf. Accessed on December 7, 2017.
17. Wang C, Nieschlag E, Swerdloff R, et al. International Society for the Study of Aging Male, the International Society of Andrology, the European Association of Urology, the European Academy of Andrology, and the American Society of Andrology (ISSAM/ISA/EAU/EAA/ASA). Investigation, treatment, and monitoring of late-onset hypogonadism in males: recommendations. Eur Urol. 2009; 55(1):121-130.

Websites for Additional Information

1. National Institute on Aging. Menopause. Last update June 10, 2015. Available at: https://www.nia.nih.gov/health/publication. Accessed on December 7, 2017.
2. National Institutes of Health. Menopausal Hormone Therapy Information. Last reviewed April 25, 2016. Available at: http://www.nih.gov/PHTindex.htm. Accessed on December 7, 2017.

Index

Document History

Status	Date	Action
Reviewed	02/23/2018	Behavioral Health Subcommittee review.
Revised	01/25/2018	Medical Policy & Technology Assessment Committee (MPTAC) review. The document header wording updated from “Current Effective Date” to “Publish Date.” Reformatted MN criteria for symptomatic hypogonadism (primary or secondary) to include examples of primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).

		Added the term, “Gender Incongruence” to the Clinical Indications section. Expanded the Discussion section with recommendations from the 2017 Endocrine Society updated guidelines for Endocrine Treatment of Gender Dysphoric/Gender Incongruent Persons. Added information from the APA DSM-5 related to gender psychology. Updated Definitions, Rationale, Background, References and Websites sections.
Revised	08/03/2017	MPTAC review. Reformatted MN section adding header to separate the MN indications. Updated Rationale, Background, Coding, References and Websites sections.
Revised	08/04/2016	MPTAC review. Added MN criteria for initiation and continuation of subcutaneous hormone therapy for treatment of males with congenital or acquired endogenous androgen absence or deficiency associated with primary or secondary hypogonadism. Added MN statement for subcutaneous testosterone implants for treatment of delayed puberty and transgender individuals. Revised I/NMN statement for subcutaneous hormone implants (estrogen alone OR estrogen combined with testosterone). Updated Description, Discussion, Definitions, References and Websites. Updated Coding section to include 10/01/2016 ICD-10-CM changes and removed ICD-9 codes.
Reviewed	08/06/2015	MPTAC review. Updated Rationale, Background, References and Websites.
Reviewed	08/14/2014	MPTAC review. Description, Rationale, Background and Websites updated.
Reviewed	08/08/2013	MPTAC review. Updated Description, Background, References and Websites.
Reviewed	08/09/2012	MPTAC review. Updated References, Coding and Websites.
Reviewed	08/18/2011	MPTAC review. Definitions, References and Websites updated.
Reviewed	08/19/2010	MPTAC review. Websites and References updated.
Reviewed	08/27/2009	MPTAC review. References updated.
Revised	08/28/2008	MPTAC review. Updated review date, coding and references. Additional investigational and not medically necessary statement added. Title updated to include “Subcutaneous.”
	02/21/2008	The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC.
Reviewed	08/23/2007	MPTAC review. Clarified description on hormone replacement implants. Updated rationale, background, references and websites. No changes to position.
Reviewed	09/14/2006	MPTAC review. Updated review date, coding and references. No changes to position.
Revised	09/22/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	**Last Review Date**	**Document Number**	**Title**
Anthem, Inc.			No prior document
WellPoint Health Networks, Inc.	9/23/2004	8.09.01	Hormone Implants